II. REMARKS

Claims **56, 57, 59-66, 69, 70, 73-79, 88** and **90** were pending and examined in the subject application and stand now variously rejected. By this amendment and response, claims **56, 57,** and **62** have been amended and new claims **91** to **94** have been added. Claims **58** to **61** and **63** to **90** have been cancelled without prejudice or disclaimer. Applicants respectfully reserve the right to file one or more continuation applications related to the same subject matter as the canceled claims, or the claims as previously presented.

Support for the amendments to claims **56, 57, 62, 93 and 94** is found in the specification on pages 21, 30, 31, 45, 46, 70 and 71. Accordingly, the amendments to the claims do not raise an issue of new matter and entry thereof is respectfully requested. New claims **91** and **92** are supported on pages 22 through 27. The addition of these claims does not raise an issue of new matter and entry thereof is respectfully requested.

In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the rejections is respectfully requested. Claims **56, 57** and **62** as amended and new claims **91** to **94** are presented for examination.

Summary of Examiner Interview

Applicants' representative thanks the Examiner for the courtesy extended during the June 12, 2007 personal interview. Applicants' representative has reviewed the Interview Summary issued by the Office. In accordance with the procedure outlined in M.P.E.P. § 713.04, the following is Applicants' summary of the interview.

1. A brief nature of any exhibits shown or any demonstration conducted: No exhibits were shown nor was any demonstration conducted.

2. An identification of the claims discussed: All pending claims were discussed with particular emphasis on claims **56, 57** and **62** and the evidence of record in support of their compliance with 35 U.S.C. § 112, first and second paragraphs.

3. An identification of the prior art discussed: Prior art was not discussed as no art, other than the assignee's copending applications that have been raised against the pending claims.

5. A brief description of the general thrust of the principal arguments presented to the Examiner: During the interview, the undersigned attorney advised the Office that the grounds for rejection were improper as the evidence of record shows that the claims are commensurate with the record. Applicants' attorney discussed the reasons why the claims are enabled throughout their full scope. For example, Applicants have shown the mechanism of action of the claimed compounds, namely that they are prodrugs activated by thymidylate synthase (TS). TS is known to be overexpressed in certain cancer cells and the claims are specific to cells endogenously overexpressing TS. Because the records shows that TS causes the conversion of the prodrug to the toxic metabolite, there is an expectation that the growth or proliferation of any cell overexpressing TS would be inhibited by contacting this cell with a compound defined in the claims.

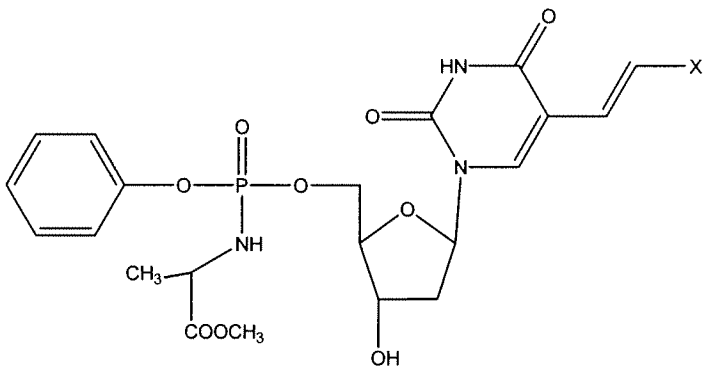
6. A general indication of any other pertinent matters discussed: Applicants' attorney reviewed the subject matter of the present application in relation to the copending co-owned applications that have been cited by the Examiner under obviousness-type double patenting and pointed out for the Examiner's convenience the commonalities and differences among the applications.

7. If appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the Examiner: Applicants' attorney offered claim amendments but the Examiner did not opine the acceptability of these offered claim amendments to remove the outstanding rejections.

Status of the Claims

After entry of the proposed amendments, claims **56, 57, 62** and **91** to **94** are pending in the subject application. Independent, amended claim **62** is directed to a compound having the

general structure:



or its pharmaceutically acceptable salt, ester or ether, wherein X is -Cl, or I, and wherein the compound may be in any enantiomeric, diastereomeric, α-anomeric form, β-anomeric form or stereoisomeric form, wherein the stereoisomeric form consists of a D-form and an L-form.

New claims **91** and **92** depend on claim **62** and are directed to compositions containing a compound of claim **62**.

Amended claims **56** and **57** are directed to methods of inhibiting the proliferation of specified cancer cells (claim **56**) or to methods for treating specified cancers (claim **57**) by the use of the compounds of claim **62** or the compositions of claims **91** and **92**. New claims **93** and **94** limit the methods of claims **56** and **57** to breast cancer and colon cancer, respectively.

Claim Informalities

Claim **62** stands objected to for misspelling of diasteriomeric. The claim has been amended to "diastereomeric" thereby removing this ground for objection. Reconsideration and withdrawal of the objection is therefore respectfully requested.

35 U.S.C. § 112, First Paragraph

Claims **56** and **57** remain rejected under 35 U.S.C. § 112, first paragraph for allegedly lacking support in the specification. Briefly, the Examiner stated that with respect to method claims **56** and **57**, the specification does not support the treatment of all diseases encompassed by the terms cancer, autoimmune disorder and inflammatory conditions.

Claims **56**, **57**, **59-61** and **88** stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter not enabled by the specification.

Applicants respectfully traverse the grounds for rejection for the reasons which follow.

With respect to claims **56** and **57**, Applicants first note that the claims are not directed to the treatment of all diseased encompassed by the terms cancer, autoimmune disorder and inflammatory conditions. The examined claims were directed to inhibiting the proliferation of neoplastic cells that overexpress thymidylate synthase (TS). The overexpression of TS has been noted in many cancers and autoimmune disorders. (See, for example, Table 4 on page 32, and pages 30 and 31 of the application papers.) Additional evidence of the connection between overexpression of TS and the pathological phenotype has been previously submitted to the Examiner, for example, in the papers filed by Applicants on June 1, 2004 and August 28, 2006.

Moreover, Applicants reiterate that the Office has not presented a *prima facie* case because the record does not provide technically supported statements to question the evidence of record, taken as whole. That burden always lies with the Office:

> "In order to make a rejection [under 35 U.S.C. § 112, first paragraph], the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention

> in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. 439 F.2d at 224, 169 USPQ at 370."

See M.P.E.P. § 2164.04.

The Office's remarks in support of the rejection are substantially limited to the number of working examples provided by Applicants' specification.[1] For example on page 4 of the outstanding Action, the Office argued that the specification does not enable the claims because:

> "E. The level of predictability is low because only two closely related neoplastic disease conditions have been shown to be effectively inhibited by a phosphoramidated BVDU compound.
>
> F. The amount of direction provided by the inventor is limited to showing how to make and administer a single phosphoramidated BVDU compound to cause inhibition of two closely related neoplastic disease conditions.
>
> G. The existence of working examples is limited to a single compound administered to cells in vitro culture infected by two closely related carcinomas.
>
> H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure would be excessive because the disclosure does not describe how to effectively treat anything other than carcinoma in humans breast and colon tissue."

M.P.E.P. § 2164.02 cautions against an Examiner's sole reliance upon the number of working examples in rejecting a claim for allegedly lacking enablement.

> "The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims."

The Office also cited *Ex parte Balzarini*, 21 USPQ2d 1892 (BPAI 1992)[2], as legal support for the rejection. Applicants submit that the facts underlying this decision distinguish the holding and make reliance on this decision improper in support of the present rejection.

The claims under consideration in *Balzarini supra*, were to the use of certain claimed compounds to treat retroviral infections. More particularly, the claims were directed to methods to treat or inhibit HIV infections and to treat diseased caused by HIV, most notably AIDS and AIDS-related disorders. The Office initially rejected the claims under 35 U.S.C. § 101 and § 112, first paragraph on the ground that the evidence of the *in vitro* evidence of record did not support the use of the compounds *in vivo*. However, unlike the facts of the present application, the Office supplied a published technical opinion supporting the rejection that the *in vitro* evidence in the specification (further supported by an opinion declaration) was insufficient to establish enablement of the methods *in vivo*. In affirming the Office's rejections, the Board noted that:

> "It is apparent from this reference [Sandstrom, supplied by the Office in rebuttal of the statements made by Applicants] that in 1987 those skilled in this art did not associate successful *in vitro* treatment of HIV infected human cells with any probability of achieving success in *in vivo* treatment of this disease. While the *in vitro* testing performed on these anti-viral compounds appears to be useful as a screening tool in order to determine which of these anti-viral compounds are

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[1] It also does not address the supplemental evidence of record provided to the Office.

[2] See page 5 of the Office Action issued April 10, 2007.

> candidates for further testing to determine if they possess *in vivo* utility, the *in vitro* tests were not predictive of *in vivo* efficacy. As set forth on page 386 of Sandstrom in the conclusion section, the development of *in vitro* assay systems is important in this area so that "national selection of potential anti-viral compounds can be made" (emphasis added).
>
> The difficulty in concluding that a specific anti-viral compound will be useful *in vivo* in this field solely from *in vitro* testing is particularly seen from the results set forth in Sandstrom for the anti-viral compounds suramin and AZT. Suramin is a known antiviral agent which was demonstrated by Mitsuya in 1985 to protect human T-cells against infectivity and cytopathic effects of HIV *in vitro*. The authors state in the second full paragraph of this article their belief that the *in vitro* results reported in this reference provide a rationale for a "carefully-monitored experimental trial" of this anti-viral compound in patients with AIDS to determine whether suramin does inhibit HIV replication *in vivo*. Thus, even the researchers who performed the work establishing the *in vitro* efficacy of suramin against HIV infected human cells were unwilling to predict that such *in vitro* work provided a basis to conclude that this compound would have *in vivo* efficacy."
>
> *Id.* at 1895.

In contrast to the facts of *Balzarini, supra*, Applicants are neither claiming the treatment of retroviral infections and AIDS nor has the Office provided reasoned technical evidence why one of skill in the art would question the evidence of record showing how to make and use the claimed invention within the full scope of the claims.

Applicants are not claiming compounds or methods to treat retroviral therapy but rather methods for inhibiting the proliferation of hyperproliferative neoplastic cells (prior claim **56**), methods to treat diseases characterized by hyperproliferative neoplastic cells (prior claim **57**) and methods to treat or inhibit the growth of a cancer cell (prior claim **88**), all related in that the cells or tissue overexpress overexpressing thymidylate synthase (TS). With respect to the treatment of cancer, successful treatment of cancer is no longer considered incredible. Rather, the successful treatment of many cancers is documented and the correlation between *in vitro* and *in vivo* efficacy also has been documented. Applicants also have shown that the claimed compounds are prodrugs that are converted to the active metabolite by the enzyme TS. TS was known to be overexpressed in cancers (see Table 2 of Applicants' specification). Applicants confirmed this

overexpression. This is documented in Table 3 of commonly assigned U.S. Patent No. 6,683,061, (PTO-892 ref. AB, cited by the Examiner on page 8 of the outstanding Office Action) and Table 4 of commonly owned PCT Publication No. WO 01/07088, a copy of which was submitted to the Office with the Reply filed June 1, 2004.

In view of the above, Applicants submit that the rejection is improper and the claims as previously presented satisfied the requirement of 35 U.S.C. § 112, first paragraph (enablement).

However, as noted during the June 12, 2007 interview, without conceding the correctness of the Office's position and to advance examination, claims **56** and **57** have been amended to recite to the cancers specifically recited in the Markush group using the compounds of amended claim **62**. Support for this claim amendment is found in the specification on page 15, lines 12 to 15 and on page 30, lines 25 and 26. Support for the amendment of claim **62** to the specifically recited prodrug structures is found on pages 40 and 41 of the specification. The amended claims are presented in a sincere effort to overcome the stated grounds for rejection.

In view of the preceding amendments and remarks, reconsideration and withdrawal of all grounds for rejection is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims **56, 57** and **62** stand rejected under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Without repeating the stated grounds for rejection, Applicants submit that the amended claims address and overcome the grounds for rejecting the claims under 35 U.S.C. § 112, second paragraph. In view of the preceding amendments, reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting Rejections

The Office cited numerous grounds why the pending claims are unpatentable over Applicants' co-pending applications. Applicants respectfully defer responding to all double patenting rejections until allowable subject matter has been indicated by the Office in the subject application. Applicants respectfully request that the Examiner review these issues in light of the foregoing amendments.

In accordance with the duty of disclosure set forth in M.P.E.P. § 2001.06(b), Applicants note the following co-pending applications and issued patents for the Examiner's convenience:

1. U.S. Patent No.: 6,495,553, U.S. Serial Nos.: 11/034,036; 09/789,226; and 11/627,341;

2. U.S. Patent Nos.: 6,339,151 and 6,245,750;

3. U.S. Serial No.: 10/048,033;

4. U.S. Patent No.: 6,683,061 and U.S. Serial No.: 10/681,418;

5. U.S. Patent No.: 7,138,388 and U.S. Serial No.: 11/516,457; and

6. U.S. Serial No.: 10/119,927.

III. CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit

card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: Aug. 6, 2007

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